loxP sequence is not a part of the present invention because the specification does not discuss a Cre-lox recombination system, except when discussing the prior art. Adequate description under the first paragraph of 35 U.S.C. §112 does not require literal support for the claimed invention. Rather, it is sufficient if the originally-filed disclosure would have conveyed to one having ordinary skill in the art that an applicant had possession of the concept of what is claimed. These amendments are made simply to clarify the content of the plasmids and are not related to patentability.

Rejection of the Claims under 35 U.S.C. §112

1. Rejection of the Claims under 35 U.S.C. §112, second paragraph

Claims 2-8 and 10-25 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Page 2 of the Office Action dated December 19, 2001 stated that claims 11, 16, 17 and 22 has been amended to recite "consisting essentially of." Claims 11, 16, 17, and 22 have been amended to delete this phrase. This rejection is obviated by these amendments.

Page 3 of the Office Action requested classification regarding sequences 0 to 1 map units in the shuttle plasmid. Claims 16, 17 and 22 have been amended to recite "map units."

The Examiner also requested clarification regarding claim 15. The term "novel" has been deleted, thereby rendering this rejection moot.

The Examiner also requested clarification regarding "rapidly" producing recombinant adenoviruses. The term "rapidly" has been deleted, thereby rendering this rejection moot.

Therefore, Applicant respectfully requests that this rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

2. Rejection of the Claims under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 2-8 and 10-25 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed,

had possession of the claimed invention (*i.e.*, a written description rejection). Independent claims 11, 16, 17 and 22 have been amended. Insofar as the Examiner applies this rejection to the pending claims, it is hereby traversed.

"Lack of literal support. . . is not enough. . . to support a rejection under § 112. The test is whether the disclosure of the application relied upon reasonably conveys to a person skilled in the art that the inventor had possession of the claimed subject matter at the time of the earlier filing date." (emphasis added) *Eigelstein v. Frank*, 34 U.S.P.Q.2d 1467, 1470 (Fed. Cir. 1995); *In re Kaslow*, 217 U.S.P.Q. 1089, 1096 (Fed. Cir. 1983). The content of the drawings may also be considered in determining compliance with the written description requirement. *Kaslow* at 1096.

The Examiner states at page 30 of the Office Action dated July 5, 2001 that the amendment reciting the negative limitation "lacks a loxP sequence" is new matter. Applicant respectfully disagrees with this determination. The Examiner cited to *Ex Parte Grasselli*, 281 U.S.P.Q. 393 (Bd. App. 1983), *aff'd mem.*, 738 F.2d 453 (Fed. Cir. 1984) for the proposition that any negative limitation or exclusionary proviso must have basis in the original disclosure. Unfortunately, the *Grasselli* case is only two pages long, and does not provide any detail as to what was or was not included in the specification. The Board simply states its conclusion at the end of the case that they argued with the "Examiner's position of record that the negative limitations recited in the present claims, which did not appear in the specification as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. § 112." *Grasselli* at 394. The Board did not present any comparative analysis of the specification and the amended phrase.

A case that provides more guidance is that of *In re Wright*, 9 U.S.P.Q.2d 1644 (Fed. Cir. 1989). In the *Wright* case the Applicant attempted to amend the claims to recite "which is distributed upon said support but not permanently fixed thereto." *Id.* at 1650. The *Wright* Examiner stated the following:

> It is the position of the Examiner that new limitation to microcapsules having the term "not permanently fixed" is not supported in the disclosure and therefore is new matter. The words "not permanently fixed" do not appear in the specification as originally filed and it is questionable whether Appellant's specification, unequivocally teaches the absence of permanently fixed microcapsules. *Id.*

The Board analyzed the situation slightly differently, but arrived at the same conclusion, after reiterating the long-standing rule of many courts that the claimed invention does not have to be described in *ipsis verbis* in order to satisfy the description requirement of § 112. The specification as originally filed must convey clearly to those skilled in the art the information that the Applicant has invented the specific subject matter later claimed. "When the original specification accomplishes that, regardless of how it accomplishes it, the essential goal of the description requirement is realized." *Id.* (emphasis in original). The Court goes on to state that "[i]n deciding the issue, the specification as a whole must be considered. The claimed subject matter need not be described *in haec verba* in the specification in order for that specification to satisfy the description requirement. The fact, therefore, that the exact words here in question, "not permanently fixed" are not in the specification is not important." *Id.* The Court concluded that it was of the essence of the original disclosure that the microcapsules are "not permanently fixed" to their various supports. The Examiner was, therefore, wrong in this underlying premise that the limitation added to the claim by amendment contained "new matter."

The present situation is analogous to that in *Wright*. Applicant concedes that the specific words "lack a loxP sequence" do not appear in the specification just as the words "not permanently fixed" did not appear in the *Wright* specification. One having ordinary skill in the art upon reading the full disclosure and examination of the drawings would recognize that Applicants had developed a new adenovirus-based cloning system that was an improvement over the known systems, including the Cre-lox system, and that it worked without the need for loxP sequencing in the vectors (*See, e.g.*, Example 4). A skilled artisan would recognize that a loxP sequence is not a part of the present invention.

The specification specifically discusses the Cre-lox recombination system in the Background of the Invention (see p. 2, line 25 to p. 3, line 9), where it mentions that there are drawbacks to the Cre-lox recombination system. The presence of loxP sequences are essential to the Cre-lox recombination system. No where in the present specification, besides the passage discussed above where problems of the available methods were mentions, are loxP sequences mentioned. When one with skill in the art evaluated the full specification, the skilled worker would clearly recognize that loxP was not a part of the present invention. For instance, Figures 1

and 2 depict the generation of example shuttle and backbone plasmids that are devoid of loxP sequences. Also, the Examples discussed at pages 8-11 of the present specification are devoid of loxP sequences. The working examples indicated that these backbones and shuttles that do not contain loxP sequences are effective at generating recombinant adenovirus. Thus, it is clear from the examination of the full specification that the inventors were in possession of a cloning system that lacked loxP sequences and in fact specifically desired to generate an improved cloning system that did not require the presence loxP sequences and the Cre enzyme.

Applicant therefore requests that the Examiner withdraw the rejection under 35 U.S.C. § 112.

§103 Rejection of the Claims

1. Aoki et al. in view of Chinnadurai et al.

Claims 4, 5, 10, 11 and 13-25 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Aoki *et al.* (Molecular Medicine, 5: 224-231 (1999)) and Chinnadurai *et al.* (Journal of Virology, 32(2): 623-628 (1979)). The present independent claims recite a shuttle plasmid comprising Ad sequences from 0 to 1 and 9.2 to 16.1 map units of an Ad genome and lacking a loxP sequence (claim 11) and a cloning system that includes this shuttle plasmid and an Ad backbone plasmid comprising an Ad genome lacking map units 0 to 9.2 and lacking a loxP sequence (claim 16), host cells comprising this cloning system (claim 17), and a method of using the cloning system (claim 22).

Applicant continues to assert that the Examiner has not established a *prima facie* case of obviousness. In order to establish a *prima facie* cases of obviousness, three factors must be met. First, the references themselves must teach or suggest all the limitations of the claims. Second, there must be a reasonable expectation of success at the time the invention was made. Third, the prior art must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference, or to combine references. Applicant respectfully asserts that the Examiner has not met all of these three requirements for the pending claims.

Chinnadurai *et al.* teach basic homologous recombination using Ad2 and Ad5. Chinnadurai *et al.* demonstrated that intact full-length viral genomes were infectious, and when

transfected into cells gave rise to adenovirus. They described that "the method involves the cotransfection of DNA restriction fragments with overlapping sequences from the two parental DNAs to generate in vivo recombinant DNAs resulting in infectious virus." Page 627 Discussion, 2nd sentence. Another important point is that incomplete digestion of the adenovirus genomes resulted in the production of adenovirus. Page 624, Results, third sentence states: "The low level of infectivity seen with DNA digested with EcoRI may be due to the low levels of undigested DNA." This is a diversion between Chinnadurai's discovery and the present patent application. Using adenovirus genomes for the propagation of recombinant adenovirus particles is "not practical with mixed infections of virions or intact DNAs because recombinants cannot be distinguished from the large excess of parental plaques that would be produced" (page 625, left column, last paragraph, second sentence). Digestion with restriction endonucleases still resulted in "the low level of infectivity."

The Ad backbone plasmid of the present claims, for example claim 16, differ from that discussed by Chinnadurai *et al.* in that the present plasmid is not an infectious clone of the adenovirus genome. Incomplete restriction endonuclease digestion of the backbone plasmid does not result in infectious virus. The present inventors have solved the problem of infectious virus by generating a plasmid-based clone that lacks map units 0-9.2. In addition, system of Chinnadurai *et al.* used 16.5 map units to facilitate the in vivo recombination step. In the present patent application, the inventors moved the area of recombination to units 9.2 - 16.1 and limited the region to 6.9 map units. Thus, the cloning system of the present invention is distinguishable from Chinnadurai *et al.* in several respects.

Regarding Aoki *et al.*, the Examiner concedes that Aoki *et al.* does not teach a system for generating recombinant adenovirus without the Cre-lox method. Therefore, Aoki *et al.* alone does not anticipate the present invention. Applicant asserts that there is no motivation to combine Aoki *et al.* with Chinnadurai *et al.* to arrive at the present invention.

Aoki *et al.* discuss an adenoviral vector that uses the Cre-loxP system. Specifically, the article by Aoki *et al.* teaches that map units 9.2-16.1 are not sufficient generate adenovirus. Page 226, under the Results section beginning with sentence 4, states "Cre recombinase produces the full-length recombinant adenoviral vector in vitro by intermolecular recombination between the

loxP sites in these two linearized molecules. It is not necessary to remove the un-recombined DNA, because only recombined adenoviral DNA among the four molecules in the Cre reaction mixture can give rise to adenovirus." Aoki *et al.* further discounts the role of map units 9.2 to 16.1 in the shuttle plasmid, as they were not included in Figure 1A. Aoki *et al.* argued that recombination would have to occur at the loxP sites to result in adenovirus, and without this recombination step, would not "give rise to adenovirus." Therefore Aoki *et al.*, one of extraordinary skill in the art and having known of the Chinnadurai manuscript (Aoki ref #6), taught that the transfected DNA needed to consist of a single linear strand and contain map units 0-1 and the left ITR.

The prior art does not contain some suggestion or incentive that would have motivated the skilled artisan to modify or to combine these references. The Federal Circuit in *In re Sang Su Lee*, 61 U.S.P.Q.2d 1430-1436, 1433 (Fed. Cir. 2002) has recently stated the following:

> The factual inquiry whether to combine references must be thorough and searching. *Id.* It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with. *See, e.g., Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124-25, 56 U.S.P.Q.2d 1456, 1459 (Fed. Cir. 2000) ("a showing of a suggestion, teaching, or motivation to combine the prior art references is an 'essential component of an obviousness holding'") (*quoting C.R. Bard, Inc., v. M3 Systems, Inc.*, 157 F.3d 1340, 1352, 48 U.S.P.Q.2d 1225, 1232 (Fed. Cir. 1998)); *In re Dembiczak*, 175 F.3d 994, 999, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."); *In re Dance*, 160 F.3d 1339, 1343, 48 U.S.P.Q.2d 1635, 1637 (Fed. Cir. 1998) (there must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant); *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988) ("'teachings of references can be combined only if there is some suggestion or incentive to do so.'") (emphasis in original) (*quoting ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984)).

The cited art does not provide a suggestion or motivation to combine Chinnadurai *et al.* with Aoki *et al.* The Introduction section of Aoki *et al.* discusses homologous recombination in mammalian helper cells between shuttle plasmid and an overlapping DNA of virus origin that has been rendered noninfectious. Aoki *et al.* specifically cites to Chinnadurai *et al.* regarding this

homologous recombination method. Aoki *et al.* continues, however, to state "since homologous recombination is a rare event in mammalian cells. These procedures are often unpredictable, time-consuming, and difficult to control. To circumvent these problems of efficiency and contamination of wild-type adenovirus, we proposed using Cre-loxP recombination *in vitro*." Aoki at p. 224-225. Therefore, one of skill in the art (namely, Aoki *et al.*) were aware of the teachings of Chinnadurai *et al.*, and chose to use the Cre-loxP system, and not the system of the present invention.

It is respectfully submitted that the Examiner appears to be employing hindsight to arrive at Applicant's invention in the absence of any suggestion in the cited art to take Applicant's approach. The Examiner is reminded that it is impermissible to use Applicant's specification as a template to arrive at the conclusion that the claimed invention is obvious. *In re Fritsch*, 23 U.S.P.Q.2d 1780, 1782 (Fed. Cir. 1992). To render an invention obvious, the combination of the cited art must teach or suggest the claimed invention and provide a reasonable expectation of success in preparing the claimed invention. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991); *In re O'Farrell*, 853 F.2d 894, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988).

Neither of these references, either alone or taken in combination, teach the present claimed invention. Therefore, Applicant respectfully requests that this rejection under 35 U.S.C. § 103 be withdrawn.

2. *Aoki et al. in view of Chinnadurai et al. and Krougliak et al.*

Claims 2, 3 and 6 were also rejected under 35 U.S.C. § 103(a) as being unpatentable over Aoki *et al.* and Chinnadurai *et al.*, and further in view of Krougliak *et al.* (Human Gene Therapy, 6: 1575-1586 (1995)).

Krougliak *et al.* does not remedy the deficiencies of Aoki *et al.* and Chinnadurai *et al.* There is no suggestion or motivation, either in the cited references themselves or in the knowledge generally available to an art worker, to modify the references or to combine the teachings of the references so as to arrive at the claimed invention. Pending claims 2, 3 and 6 recite a two-part cloning system; the first element being a backbone plasmid comprising map units 9.2 to 100 of an Ad genome but lacking loxP sequences, and the second element being a

shuttle plasmid comprising map units 0 to 1 and 9.2 to 16.1 of an Ad genome but lacking loxP sequences.

Krougliak *et al.* generated cell lines that could complement E1, E4 and protein IX defective adenovirus type 5 (Ad5) mutants. The plasmid system used by Krougliak *et al.* contained adenovirus sequences from the left ITR to the right ITR (*i.e.*, the full viral backbone), except for sequences encoding E1, E4 or protein IX. The intention of the deletions by Krougliak *et al.* was to provide for more space to accommodate larger inserts placed into the E1 region of the adenovirus vector and not to otherwise modify the backbone. Both Aoki *et al.* and Kroughliak *et al.* devised strategies to make recombinant adenovirus only when the intact recombinant adenovirus genome that contained map units 0-1 and the left ITR was transfected into the cell. Recombination in this region was directly refuted by Aoki *et al.* and not attempted by Kroughliak *et al.*, both of whom were extraordinarily skilled in the art.

Thus, none of these references, either alone or taken in combination, teach the present claimed invention. Therefore, Applicant respectfully requests that this rejection under 35 U.S.C. § 103 be withdrawn.

3. *Aoki et al. in view of Chinnadurai et al., Krougliak et al. and Breakfield et al.*

Claims 7 and 8 were also rejected under 35 U.S.C. § 103(a) as being unpatentable over Aoki *et al.*, Chinnadurai *et al.* and Krougliak *et al.*, and further in view of Breakfield *et al.* (U.S. 5,965,441).

Breakfield *et al.* does not remedy the shortcomings of Chinnadurai *et al.*, Aoki *et al.* and Krougliak *et al.* Breakfield *et al.* teach a hybrid vector system that incorporate elements of herpes virus and adeno-associated virus that is capable of expressing a gene product in eukaryotic cells. The Examiner admits that Breakfield *et al.* is deficient in that it does not teach an adenovirus vector. The Examiner states, however, that "one of ordinary skill in the art at the time the invention was made would have been motivated to incorporate HSV Amplicon sequences into the backbone of Aoki *et al.* to expand the host range of gene expression to dividing cells."

Again, the Examiner appears to be using hindsight to arrive at Applicant's invention, selecting aspects from four different references to attempt to piece together Applicant's invention. Even if one with skill in the art was motivated to combine these four references, when they are logically combined, one would have the Aoki *et al.* Ad vector containing a loxP sequence and the Breakfield *et al.* AAV/HSV hybrid sequences in the Krougliak *et al.* cell line (in a backbone containing the lefthand ITR). In contrast, the plasmids used in the present claimed cloning system do not contain loxP sequences or the lefthand ITR.

Thus, none of these references, either alone or taken in combination, teach the present claimed invention. Therefore, Applicant respectfully requests that this rejection under 35 U.S.C. § 103 be withdrawn.

4. Aoki et al. in view of Chinnadurai et al. and Chartier et al.

Claim 12 was also rejected under 35 U.S.C. § 103(a) as being unpatentable over Aoki *et al.* and Chinnadurai *et al.*, and further in view of Chartier *et al.* (Journal of Virology, 70(7): 4805-4810 (1996)).

Aoki *et al.* and Chinnadurai *et al.* are discussed above. Chartier *et al.* do not remedy the deficiencies of Aoki *et al.*, and Chinnadurai *et al.* Chartier *et al.* disclose the introduction of unique PacI site into and Ad5 vector.

There is no suggestion or motivation in the cited references to combine the teachings of the references so as to arrive at the claimed invention. Claim 12 recites a shuttle plasmid having Ad sequences wherein PacI restriction endonuclease sites flank either end of the Ad sequences, but wherein the plasmid lacks a loxP sequence. If Aoki *et al.*, Chinnadurai *et al.* and Chartier *et al.* are combined, one would have the Aoki *et al.* Ad vector containing a loxP sequence and the Chartier *et al.* PacI sites. In contrast, the present claimed invention does not contain loxP sequences.

Thus, none of these references, either alone or taken in combination, teach the present claimed invention. Therefore, Applicant respectfully requests that this rejection under 35 U.S.C. § 103 be withdrawn.

Conclusion

Applicants respectfully submit that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicants' attorney (612-373-6961) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

BEVERLY L. DAVIDSON *Et al.*

By their Representatives,

SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.
P.O. Box 2938
Minneapolis, MN 55402
(612) 373-6961

Date 18 March 2002 By _____

Ann S. Viksnins
Reg. No. 37,748

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231, on this 18th day of March, 2002.

Candis B. Buending
Name

_____
Signature